07:14 OCA PAD INITIATION - PROJECT HEADER INFORMATION 08/25/87

roject # G-33-U06 MOD # REV # 0
ontract # 5 R01 HL29307-06 OCA file # Status A
ontract entity GIT Prime contract #
)PI POWERS J C (DR.
SSN 366-34-6157 Unit CHEM Phone ( ) -
roject unit CHEM Unit code 02.010.136
Sponsor/Division DHHS/PHS/NIH / NATL INSTITUTE OF HEALTH
Sponsor#/division # 108 / 001
Type of document GRANT
Award period: from 87 / 08 / 01 to 88 / 07 / 31 (perf) 88 / 10 / 31 (rpts)

ponsor amount	New this change	Total to date
Contract value	$ 154085	154085
Funded	$ 154085	154085

Cost sharing # Cost sharing $
Does subcontracting plan apply? (Y/N) N
Title -
YNTHETIC ELASTASE INHIBITORS

TR project # Q5270-6A0 CTR cost sharing #

re there existing subprojects? (Y/N) N
s this a subproject? (Y/N) N Main project #
ontinuation of project # G-33-U05/Q5270-5A0 Type of research RES

oproject director name

SSN - - Unit

Coproject director name

SSN - - Unit

PROJECT ADMINISTRATION DATA

Administrative data OCA contact E. FAITH GLEASON PAD CO EFG 894-4820

Sponsor technical contact	Sponsor issuing office
DR. ZAKIR H. BENGALI	MS. MARA A. HERRON
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DIVISION OF LUNG DISEASES	GRANTS OP BR. DIV OF EXMURAL AFFAIRS
NAT. HEART, LUNG, & BLOOD INSTITUTE	NAT. HEART, LUNG, & BLOOD INSTITUTE
BETHESDA, MD 20892	BETHESDA, MD. 20892

Security class (U,C,S,TS)
Defense priority rating
supplemental sheet
Equipment title vests with Sponsor GIT X Comment follows -
INTERNAL PRIOR APPROVAL REQUIRED, IF NOT SPECIFIED IN AWARD.

Admin comments -
6TH YEAR OF CONTINUING GRANT APPROVED FOR 8 YEARS.

GEORGIA INSTITUTE OF TECHNOLOGY OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION/CLOSEOUT SHEET

Date 10/26/88

Project No. G-33-U06 School/~~Lab~~ Chem

Includes Subproject No.(s) N/A

Project Director(s) J. C. Powers ~~GTRC~~/GIT

Sponsor DHHS/PHS/NIH/ National Institute of Health

Title Synthetic Elastase Inhibitors

Effective Completion Date: 7/31/88 (Performance) 10/31/88 (Reports)

Grant/Contract Closeout Actions Remaining:

- [ ] None
- [XX] Final Invoice or Copy of Last Invoice Serving as Final
- [ ] Release and Assignment
- [ ] Final Report of Inventions and/or Subcontract:
  Patent and Subcontract Questionnaire sent to Project Director [ ]
- [ ] Govt. Property Inventory & Related Certificate
- [ ] Classified Material Certificate
- [ ] Other

Continues Project No. G-33-U05 Continued by Project No. G-33-U07

COPIES TO:

Project Director
Research Administrative Network
Research Property Management
Accounting
Procurement/~~GTRI Supply Services~~
~~Research Security Services~~
Reports Coordinator (OCA)
~~Program Administration Division~~
Contract Support Division
~~Facilities Management~~ ~~ERR~~
~~Library~~
~~GTRI~~
Project File
Other

G-22-UUD

SECTION IV PROGRESS REPORT SUMMARY	GRANT NUMBER HL 29307-07	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR Powers, James C.	PERIOD COVERED BY THIS REPORT FROM	THROUGH
APPLICANT ORGANIZATION Georgia Institute of Technology	8/01/87	7/31/88

TITLE OF PROJECT *(Repeat title shown in item 1 on first page)*
Synthetic Elastase Inhibitors

(SEE INSTRUCTIONS)

1. Specific Aims and Research Goals.

The primary goal of this research is to develop a synthetic elastase inhibitor which would be useful for the treatment of human emphysema. A variety of structures are being investigated including heterocyclic mechanism-based inhibitors and peptide transition state analogs. All of the inhibitors are being tested for specificity with other cellular proteases such as cathepsin G and the mast cell chymotrypsin-like enzymes (chymases). A secondary goal of this research is the extension of any potent inhibitor structures to cathepsin G and mast cell chymases. Any promising elastase inhibitors will be provided to other investigators for studies in animal models of emphysema. This research should lead to a better understanding of the active site structures of the serine proteases involved in connective tissue turnover, may produce clinically useful drugs for the treatment of emphysema and related diseases, is stimulating the research of medicinal chemists in pharmaceutical companies, and will provide new tools for the in vivo and in vitro study of the role of leukocyte and mast cell proteases in variety of physiological processes.

2. Research Report.

Active Site Structure and Molecular Modeling. Molecular modeling is one technology which is rapidly improving and becoming quite useful to the biochemist for the process of inhibitor design. A necessary starting point is an x-ray crystal structure of the target protease or a close relative. X-ray structures are now available for porcine pancreatic elastase and human neutrophil elastase. In addition, an increasing number of small molecule inhibitor complexes with serine proteases are becoming available.

The primary specificity pocket (S_1), in particular, is a major determinate of serine protease specificity and is most often utilized in inhibitor design. This pocket is a bumpy hydrophobic space in most serine proteases with a variety of amino acid side chains forming the surface of the pocket. The primary substrate binding subsite takes on a different size and shape in individual serine proteases due to sequence differences in this region of serine proteases.

The two neutrophil proteases (HL elastase and cathepsin G) have a long narrow S_1 pocket with carboxyl groups at the very end. In the case of HL elastase, Asp-226 points toward the interior of the protein into a region which has several water molecules trapped in the elastase structure. The front of the pocket is very narrow and hydrophobic. A similar situation occurs with cathepsin G where residue 226 is a glutamic acid residue. Construction of a cathepsin G model using the rat mast cell protease II backbone indicates that this Glu-226 would be placed in a similar environment to Asp-226 in HL elastase.

Previous studies with synthetic peptide thiobenzyl esters have shown that cathepsin G and RMCP II prefer substrates with a P_1 Phe, while HL and porcine pancreatic (PP) elastase most effectively hydrolyzed a norvaline containing substrate. Interestingly inhibitors with long hydrocarbon or fluorocarbon chains which can interact with this hydrophobic S_1 pocket are often the most effective HL elastase inhibitors.